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RESEARCH ARTICLE

High risk of peripheral ischemia in patients on dialysis without diabetes mellitus.

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ABSTRACT

Background: Patients on dialysis have an increased risk of peripheral arterial disease. This nationwide Danish cohort study describes the incidence of lower extremity amputation or revascularization in patients treated with dialysis and explores influence of diabetes mellitus and dialysis modality over time.

Methods: By individual-linkage between nationwide registries, risk of lower extremity amputation or revascularization was compared between two time periods and groups of patients treated with hemodialysis or peritoneal dialysis, with or without diabetes mellitus.

Results: We assessed risk of lower extremity amputation or revascularization in 75 419 patients with diabetes not on dialysis and 10 908 dialysis patients. Compared with the background population, hazard ratio for lower extremity amputation or revascularization associated with diabetes or treated with peritoneal dialysis without diabetes was equal, hazard ratio 12. Patients with diabetes on hemodialysis had hazard ratio 117(104-131) in the period 1997-2004 with lower hazard ratio in the later period, hazard ratio 68(60-77). For patients treated with hemodialysis with no diabetes, hazard ratio was not lower in the second time period; hazard ratio 15(13-18) vs hazard ratio 17(14-20). Hazard ratios of lower extremity amputation or revascularization were not significantly lower in patients with peritoneal dialysis and diabetes in the later period, hazard ratio 38(30-48) vs 30(23-37). For patients on hemodialysis with diabetes a lower hazard ratio was found in the later period. Patients without diabetes had almost the same risk of lower extremity amputation or revascularization over time. Patients on peritoneal dialysis had, compared to patients treated with hemodialysis, lower risk of lower extremity amputation or revascularization.

Conclusions: Patients on dialysis without diabetes had an equal or increased risk of lower extremity amputation or revascularization compared to patients with diabetes not on dialysis. Patients on dialysis with diabetes had higher risk compared to those without diabetes. Risk was higher in patients on hemodialysis compared to patients on peritoneal dialysis. Over time there was a trend towards decreased risk in dialysis patients with diabetes. The Danish programme for yearly evaluation of peripheral ischemia by podiatricians in patients with diabetes may be one of the reasons for the differences seen in risk reduction.

Keywords: Cohort study; dialysis; diabetes; peripheral vascular disease; amputation; revascularization

Introduction

There is a worldwide increase in number of patients treated with chronic dialysis[1] and in number of patients with diabetes mellitus (DM)[2].

In the state of chronic uremia, accelerated vascular aging is present with vascular calcification including atherosclerosis and arteriosclerosis[3], both leading to increased risk of peripheral ischemia with the need for revascularization procedures or amputations[4,5,6]. Even in patients with chronic kidney disease without diabetes there is a high risk of peripheral ischemia[7,8,9]. Peripheral ischemia could potentially result in lower quality of life. Therefore, it is important to describe the incidence of peripheral ischemia and risk of amputation or revascularization as well as to identify risk factors, particularly if they are modifiable.

A programme for monitoring foot status by podiatricians was established in Denmark in 1981 (personal communication) for the population of patients with diabetes mellitus (DM). The same awareness has not been given to patients treated with dialysis, but with no DM.

The aim of this large cohort study was to investigate the risk of lower extremity amputation (LEA) or surgical revascularization over time in the Danish dialysis population (hemodialysis (HD) vs peritoneal dialysis (PD)) compared to the background population stratified by presence of DM. Two time periods were chosen in order to evaluate improvement in preventive measures.

Materials and Methods:

STUDY DESIGN

Retrospective national cohort study.

Setting and participants

Persons above 18 years of age in Denmark were included at 1st of January 1997 and grouped according to +/- DM. Incident patients starting dialysis from 1st of January 1997 to 27th of January 2014 were also included. All patients on dialysis were grouped according to DM, dialysis modality PD or HD and period of inclusion 1997-2004 or 2005-2014. Patients living with a kidney transplant were excluded. Patients were followed until lower extremity amputation, -revascularization, emigration, death or end of study at 31st of December 2016. Dialysis patients were identified in the Danish Nephrology Registry. Persons with DM were identified in the National Patient Registry by ICD-10 diagnoses E10-14 6 months before inclusion or in the Danish Prescription Registry by filling a prescription of antidiabetic medication ATC MA10.

BASELINE VARIABLES AND OUTCOME

Gender and age at study start were found in the Danish Civil Registration System. Comorbidity was identified in the National Patient Registry one year before study start. Treatment with cholesterol lowering medication, platelet inhibitors or insulin was identified in the Danish Prescription Registry. Outcome was lower extremity revascularization procedures or - amputations registered in the National Patient Registry.

DATA SOURCES

Information on date of chronic renal replacement therapy start and modality was obtained from the Danish Nephrology Registry, where all patients actively treated for end-stage kidney disease (ESRD) in Denmark are registered[10].

The Danish civil registration system holds information including date of birth and death on the Danish population[11]. Information on comorbidity and revascularization procedures and amputations was identified in the National Patient Registry[12]. This contains information on all hospital admissions in Denmark including diagnoses, operations, dates, hospitals and departments since 1978 and from 1995 also information on out-patient treatment. Information on medical treatment was obtained from the Danish Register of Medicinal Product Statistics of the Danish Medicines Agency. The registry contains information on dispensed drugs from Danish pharmacies since 1995[13].

Cross-linkage between registries was possible due to the unique personal identification number assigned to all Danish citizens from birth or immigration.

ETHICAL CONSIDERATIONS

The study was approved by the Danish Data Protection Agency.

STATISTICAL ANALYSIS

Baseline characteristics were given for persons +/- DM and for dialysis patients furthermore in two time periods 1997-2004 and 2005-2014 with percentages, medians and interquartile ranges where appropriate.

Incidence rates were standardized according to gender and age using five age groups with the direct method and the Danish background population as reference. The age strata 18-39 years, 40-49 years, 50-59 years, 60-69 years and +70 years of age were used.

Test for interaction was performed and if present, appropriate stratification was done. There was a significant interaction between treatment group and age, gender, previous revascularization, peripheral vascular disease or amputation, gastrointestinal ulcer, cardiovascular disease, rheumatic disease, ischemic heart disease, chronic heart failure, obstructive pulmonary disease, use of cholesterol lowering drugs and platelet inhibitors. Though, none appeared to influence the risk of lower extremity revascularization or amputation.

Cox proportional hazards models with revascularization and amputation of the lower extremity as outcome were fitted to the data. Stepwise adjustment was made for gender, age, comorbidity, prior revascularization or amputation and drug use. Proportional hazards were checked graphically and proportional hazards assumption was met. Sensitivity analysis with lower extremity amputation as lone outcome was performed. Analyses were performed using SAS version 9.4, SAS Institute Inc.

Results

A total of 75 419 patients with diabetes not on dialysis and 10 908 patients on dialysis were included. Tables 1A and 1B show baseline characteristics of the background population and patients with and without DM in Denmark according to dialysis modality in the two time periods, respectively. Patients with DM or treated with dialysis were older than the background population. Overall, patients had a greater number of comorbidities

if treated with dialysis, regardless of modality and those with DM had even more, besides DM, than those without DM. There was a trend towards higher age in all dialysis patients in the late period.

Table 1A Baseline characteristics of patients with and without diabetes in Denmark between 1997 and 2004, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients).

	No diabetes and not on dialysis (n=4 156 293)		Diabetes mellitus and not on dialysis (n=75 419)		Peritoneal dialysis and no diabetes mellitus (n=581)		Peritoneal dialysis and diabetes mellitus (n=201)		Haemodialysis and no diabetes mellitus (n=3 217)		Haemodialysis and diabetes mellitus (n=1 139)	
Characteristic												
Socio-demographic												
Age *years*	45.2	31.2-60.1	63.3	50.4-73.9	60.6	49.6-70.4	58.7	47.9-67.4	66.7	54.9 -74.6	62.3	51.7-70.8
Sex *(men)*	2 082 392	50.1	39 739	52.7	350	60.2	137	68.2	2 009	62.5	730	64.1
Clinical												
Comorbidity												
Myocardial infarction	8 536	0.2	1 091	1.5	25	4.3	17	8.5	136	4.2	72	6.3
Congestive heart failure	11 992	0.3	1 929	2.6	48	8.3	29	14.4	323	10.0	178	15.6
Peripheral vascular disease	9 938	0.2	1 584	2.1	37	6.4	17	8.5	285	8.9	119	10.5
Cerebrovascular disease	4 820	0.1	532	0.7	4	0.7	3	1.5	62	1.9	32	2.8
Chronic pulmonary disease	16 130	0.4	934	1.2	19	3.3	3	1.5	181	5.6	39	3.4
Rheumatic disease	6 953	0.2	383	0.5	14	2.4	<3	<1	66	2.1	17	1.5
Peptic ulcer disease	16 549	0.4	890	1.2	19	3.3	5	2.5	141	4.4	50	4.4
Liver disease	3 295	0.1	346	0.5	4	0.7	<3	<1	53	1.7	22	1.9
Hemi –or paraplegia	840	<0.1	47	0.1	<3	<1	<3	<1	12	0.4	<3	<1
Solid malignant tumors	32 875	0.8	1 523	2.0	18	3.1	6	3.0	261	8.1	47	4.1
Leukemia	1 170	<0.1	82	0.1	<3	<1	<3	<1	8	0.3	<3	<1
Lymphoma	2 111	0.1	109	0.1	11	1.9	<3	<1	109	3.4	4	0.4
Metastatic solid tumor	1 200	<0.1	49	0.1	<3	<1	<3	<1	12	0.4	3	0.3
Lower extremity revascularization procedures and amputations	2 601	0.1	785	1.0	4	0.7	8	4.0	38	1.2	57	5.0
Medication												
Platelet inhibitors	148 233	3.6	13 793	18.3	118	20.3	81	40.3	794	24.7	425	37.3
Cholesterol lowering medication	26 358	0.6	2 130	2.8	92	15.8	66	32.8	363	11.3	283	24.9
Insulin	0	0	29 797	39.5	0	0	138	68.7	0	0	688	60.4

Values are presented as median (interquartile range) or numbers (percentage)

Table 1B. Baseline characteristics of patients with and without diabetes in Denmark between 2005 and 2014, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients).

	No diabetes and not on dialysis (n=4 156 293)		Diabetes mellitus and not on dialysis (n=75 419)		Peritoneal dialysis and no diabetes mellitus (n=795)		Peritoneal dialysis and diabetes mellitus (n=338)		Haemodialysis and no diabetes mellitus (n=3 190)		Haemodialysis and diabetes mellitus (n=1 447	
Characteristic												
Socio-demographic												
Age *years*	45.2	31.2-60.1	63.3	50.4-73.9	65.5	54.8-75.0	63.1	52.7-72.1	69.1	58.7 -77.6	67.0	58.0-74.5
Sex *(men)*	2 082 392	50.1	39 793	52.7	500	62.9	219	64.8	2 028	63.6	968	66.9
Clinical												
Comorbidity												
Myocardial infarction	8 536	0.2	1 091	1.5	24	3.0	13	3.9	156	4.9	102	7.1
Congestive heart failure	11 992	0.3	1 929	2.6	67	8.4	34	10.1	349	11.0	276	19.1
Peripheral vascular disease	9 938	0.2	1 584	2.1	30	3.8	31	9.2	287	9.0	152	10.5
Cerebrovascular disease	4 820	0.1	532	0.7	11	1.4	6	1.8	54	1.7	35	2.4
Chronic pulmonary disease	16 130	0.4	934	1.2	35	4.4	15	4.4	229	7.2	109	7.5
Rheumatic disease	6 953	0.2	383	0.5	17	2.1	4	1.2	59	1.9	15	1.0
Peptic ulcer disease	16 549	0.4	890	1.2	14	1.8	11	3.3	155	4.9	65	4.5
Liver disease	3 295	0.1	346	0.5	11	1.4	<3	<1	71	2.2	25	1.7
Hemi –or paraplegia	840	<0.1	47	0.1	<3	<1	<3	<1	9	0.3	<3	<1
Solid malignant tumors	32 875	0.8	1 523	2.0	41	5.2	10	3.0	284	8.9	63	4.4
Leukemia	1 170	<0.1	82	0.1	<3	<1	<3	<1	13	0.4	3	0.2
Lymphoma	2 111	0.1	109	0.1	11	1.4	<3	<1	124	3.9	17	1.2
Metastatic solid tumor	1 200	<0.1	49	0.1	<3	<1	<3	<1	5	0.2	<3	<1
Lower extremity revascularization procedures and amputations	2 601	0.1	785	1.0	2	0.3	9	2.7	58	1.8	72	5.0
Medication												
Platelet inhibitors	148 233	3.6	13 793	18.3	275	34.6	191	56.5	1 111	34.8	833	57.6
Cholesterol lowering medication	26 358	0.6	2 130	2.8	283	35.6	241	71.3	982	30.8	926	64.0
Insulin	0	0	29 797	39.5	0	0	252	74.6	0	0	950	65.7

Values are presented as median (interquartile range) or numbers (percentage)

There was no difference in vascular disease such as myocardial infarction (MI), heart failure, cerebrovascular disease at baseline over time. There was a trend of higher prevalence at baseline of peripheral arterial disease (PAD) in dialysis patients with DM and HD-patients compared to PD-patients.

More revascularizations and amputations were present at baseline in patients included in the later period. The use of platelet inhibitors and cholesterol lowering medication at baseline was higher in dialysis patients in the later period.

Tables 2A and 2B show incidence rates of lower extremity revascularization procedures (LER) and lower extremity amputations (LEA) from 1997-2004 and 2005-2014 according to dialysis modality and presence of DM. Figure 1 shows cumulative incidence curves for LEA with death as competing end point. The curves show the overall higher incidences of LEA's if on dialysis and having DM. The incidences were lower in the later time period for both modalities of dialysis, more in PD. Patients with no DM had no difference in LEA in the two time periods.

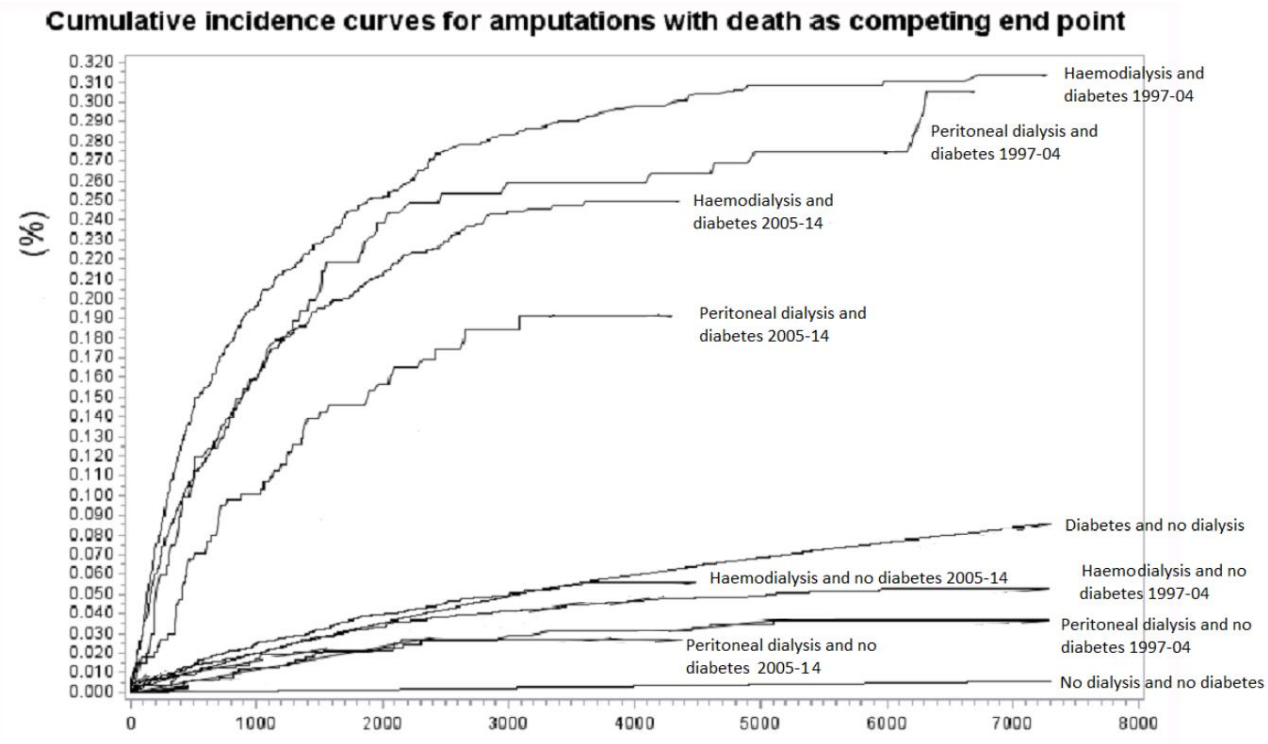

Figure 1: Cumulative incidence curves for amputations with death as competing end-point.

Table 2A Median follow-up time and incidence rates of death, emigration and lower extremity amputations and revascularization procedures in patients with and without diabetes in Denmark between 1997 and 2004, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients)

	No diabetes and not on dialysis (n=4 156 293)		Diabetes mellitus and not on dialysis (n=75 419)		Peritoneal dialysis and no diabetes mellitus (n=581)		Peritoneal dialysis and diabetes mellitus (n=201)		Haemo-dialysis and no diabetes mellitus (n=3 217)		Haemo-dialysis and diabetes mellitus (n=1 139)	
Follow-up months *median (IQR)*	239.5	(227.0-239.5)	122.2	(48.6-239.5)	59.5	(21.6-167.0)	32.7	(13.1-69.5)	40.9	(12.3-96.4)	22.6	(8.0-52.4)
Total numbers												
Death		968 375		44 801		365		112		4 244		667
Lower extremity revascularization procedures and amputations		58 765		8 367		47		68		364		430
Emigration		64 237		886		4		<3		12		<3
Crude incidence rates *per 1 000 py (95% CI)*												
Death	13	(13-14)	54	(53-54)	83	(75-92)	113	(92-134)	141	(136-147)	179	(165-192)
Lower extremity revascularization procedures and amputations	1	(1-1)	10	(10-10)	11	(8-14)	68	(52-85)	21	(19-23)	115	(104-126)
Emigration	1	(1-1)	1	(1-1)	1	(0-2)	0	0	1	(0-1)	1	(0-1)
Age-standardized incidence rates *per 1000 py (95% CI)*												
Death	14	(14-14)	31	(31-31)	91	(80-101)	125	(99-151)	103	(99-108)	154	(141-166)
Lower extremity revascularization procedures and amputations	1	(1-1)	7	(7-7)	10	(7-13)	68	(50-85)	17	(15-19)	104	(93-114)
Emigration	1	(1-1)	2	(1-2)	1	(0-2)	0	0	1	(0-2)	0	(0-1)

Abbreviations: IQR = interquartile range; py = person-years; CI = confidence interval
[1] Excluding Denmark

Table 2B Median follow-up time and incidence rates of death, emigration and lower extremity revascularization procedures in patients with and without diabetes in Denmark between 2005 and 2014, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients)

	No diabetes and not on dialysis (n=4 156 293)		Diabetes mellitus and not on dialysis (n=75 419)		Peritoneal dialysis and no diabetes mellitus (n=795)		Peritoneal dialysis and diabetes mellitus (n=338)		Haemo-dialysis and no diabetes mellitus (n=3 190)		Haemo-dialysis and diabetes mellitus (n=1 447)	
Follow-up months *median (IQR)*	239.5	(227.0-239.5)	122.2	(48.6-239.5)	47.5	(27.8-81.6)	34.7	(14.5-58.0)	39.9	(13.7-70.1)	27.7	(9.7-51.8)
Total numbers												
Death		968 375		44 801		380		185		2 078		865
Lower extremity revascularization procedures and amputations		58 765		8 367		41		72		281		404
Emigration		66 022		866		<3		<3		9		3
Crude incidence rates *per 1 000 py (95% CI)*												
Death	13	(13-14)	54	(53-54)	103	(103-113)	158	(135-180)	167	(160-174)	206	(192-219)
Lower extremity revascularization procedures and amputations	1	(1-1)	10	(10-11)	11	(8-15)	61	(47-75)	23	(20-25)	96	(87-105)
Emigration	1	(1-1)	1	(1-1)	1	(0-1)	0	0	1	(0-1)	1	(0-2)
Age-standardized incidence rates *per 1000 py (95% CI)*												
Death	14	(14-14)	31	(31-31)	109	(96-122)	165	(137-193)	134	(127-140)	182	(167-196)
Lower extremity revascularization procedures and amputations	1	(1-1)	7	(7-8)	11	(7-15)	60	(44-76)	18	(16-20)	91	(81-102)
Emigration	1	(1-1)	2	(2-2)	1	(0-2)	0	0	1	(0-2)	0	(0-1)

Abbreviations: IQR = interquartile range; py = person-years; CI = confidence interval
[1] Excluding Denmark

Table 3. Hazard ratios for lower extremity revascularization procedures and amputations in patients with and without diabetes in Denmark between 1997 and 2014, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients) and time period of starting dialysis (1997-2004 and 2005-2014)

	Diabetes and not on dialysis[1]		Peritoneal dialysis and no diabetes mellitus 1997-2004[1]		Peritoneal dialysis and diabetes mellitus 1997-2004[1]		Haemodialysis and no diabetes mellitus 1997-2004[1]		Haemodialysis and diabetes mellitus 1997-2004[1]		Peritoneal dialysis and no diabetes mellitus 2005-2014[1]		Peritoneal dialysis and diabetes mellitus 2005-2014[1]		Haemodialysis and no diabetes mellitus 2005-2014[1]		Haemodialysis and diabetes mellitus 2005-2014[1]	
Model [2]	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
1. Unadjusted	12.7	12.4-13.0	13.9	10.4-18.5	89.5	70.5-113.5	27.7	24.9-30.7	153.7	139.7-169.0	15.3	11.2-20.7	83.7	66.4-105.4	30.9	27.5-34.7	131.1	118.8-144.6
2. Demographic	9.7	9.5-10.0	15.3	11.5-20.3	106.7	84.1-135.4	25.3	22.8-28.0	152.0	138.2-167.3	17.6	12.9-23.8	102.2	81.1-128.8	30.5	27.1-34.3	134.7	122.0-148.6
3. Peripheral revascularization and amputation	9.2	9.0-9.4	15.3	11.5-20.4	93.4	73.6-118.5	23.0	20.8-25.5	117.1	106.3-129.0	16.9	12.4-23.0	91.5	72.6-105.4	24.9	22.1-28.0	90.0	81.2-99.4
4. Comorbidity	8.5	8.3-8.7	10.6	7.9-14.1	57.2	45.1-72.6	13.3	11.9-14.7	75.6	68.5-83.4	10.9	8.0-14.9	60.3	47.8-76.0	12.8	11.4-14.5	46.9	42.2-52.0
5. Medication	7.5	7.4-7.7	8.1	6.1-10.8	37.8	29.8-48.0	10.7	9.6-11.9	57.6	52.1-63.6	6.5	4.8-8.9	29.5	23.3-37.3	8.3	7.3-9.4	25.9	23.3-28.8

Abbreviations: HR = hazard ratio; CI = confidence interval
[1] Reference used is persons without diabetes and not on dialysis
[2] Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: further adjusted for peripheral revascularization procedures and amputation before study start. Model 4: further adjusted for comorbidity. Model 5: further adjusted for treatment before study start with cholesterol lowering medication and platelet inhibitors.

Table 4. Hazard ratios for lower extremity amputations in patients with and without diabetes in Denmark between 1997 and 2014, according to dialysis modality (patients not on dialysis, incident haemodialysis patients and incident peritoneal dialysis patients) and time period of starting dialysis (1997-2004 and 2005-2014)

	Diabetes and not on dialysis[1]		Peritoneal dialysis and no diabetes mellitus 1997-2004[1]		Peritoneal dialysis and diabetes mellitus 1997-2004[1]		Haemo-dialysis and no diabetes mellitus 1997-2004[1]		Haemo-dialysis and diabetes mellitus 1997-2004[1]		Peritoneal dialysis and no diabetes mellitus 2005-2014[1]		Peritoneal dialysis and diabetes mellitus 2005-2014[1]		Haemo-dialysis and no diabetes mellitus 2005-2014[1]		Haemo-dialysis and diabetes mellitus 2005-2014[1]	
Model [2]	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
1. Unadjusted	24.3	23.6-25.0	15.5	10.1-23.8	184.8	142.8-239.1	29.9	25.7-34.9	290.1	261.3-323.0	17.4	11.1-27.3	166.4	128.6-215.5	40.5	34.5-47.5	260.7	233.7-290.8
2. Demographic	18.5	18.0-19.0	17.7	11.5-27.1	224.4	173.4-290.5	27.8	23.8-32.4	300.0	269.7-333.7	21.0	13.4-33.0	216.2	167.0-280.0	41.1	35.0-48.3	280.5	251.4-313.0
3. Peripheral revascularization and amputation	17.6	17.1-18.1	17.8	11.6-27.3	203.7	157.4-263.7	25.3	21.7-29.5	242.7	218.0-270.3	20.5	13.1-32.2	196.0	151.4-253.9	34.7	29.5-40.7	200.8	179.6-224.6
4. Comorbidity	16.5	16.0-17.0	13.4	8.7-20.6	146.6	113.1-189.9	17.0	14.5-19.8	176.7	158.3-197.3	14.3	9.1-22.5	144.0	111.1-186.6	20.7	17.6-24.4	118.7	105.6-133.4
5. Medication	12.4	12.0-12.8	12.0	7.8-18.4	80.8	62.2-105.0	15.0	12.8-17.5	116.5	103.9-130.7	11.2	7.1-17.5	72.0	55.1-94.2	16.6	14.1-19.6	67.8	59.6-77.1

Abbreviations: HR = hazard ratio; CI = confidence interval
[1] Reference used is persons without diabetes and not on dialysis
[2] Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: further adjusted for peripheral revascularization procedures and amputation before study start. Model 4: further adjusted for comorbidity. Model 5: further adjusted for treatment before study start with cholesterol lowering medication, insulin and platelet inhibitors.

Figure 2 shows cumulative incidence curves for LEA and LER with death as competing end point. The curves show a clear difference between dialysis modalities and between patients with and without DM, the latter having more interventions than patients without DM. The two time periods differ as in Figure 1.

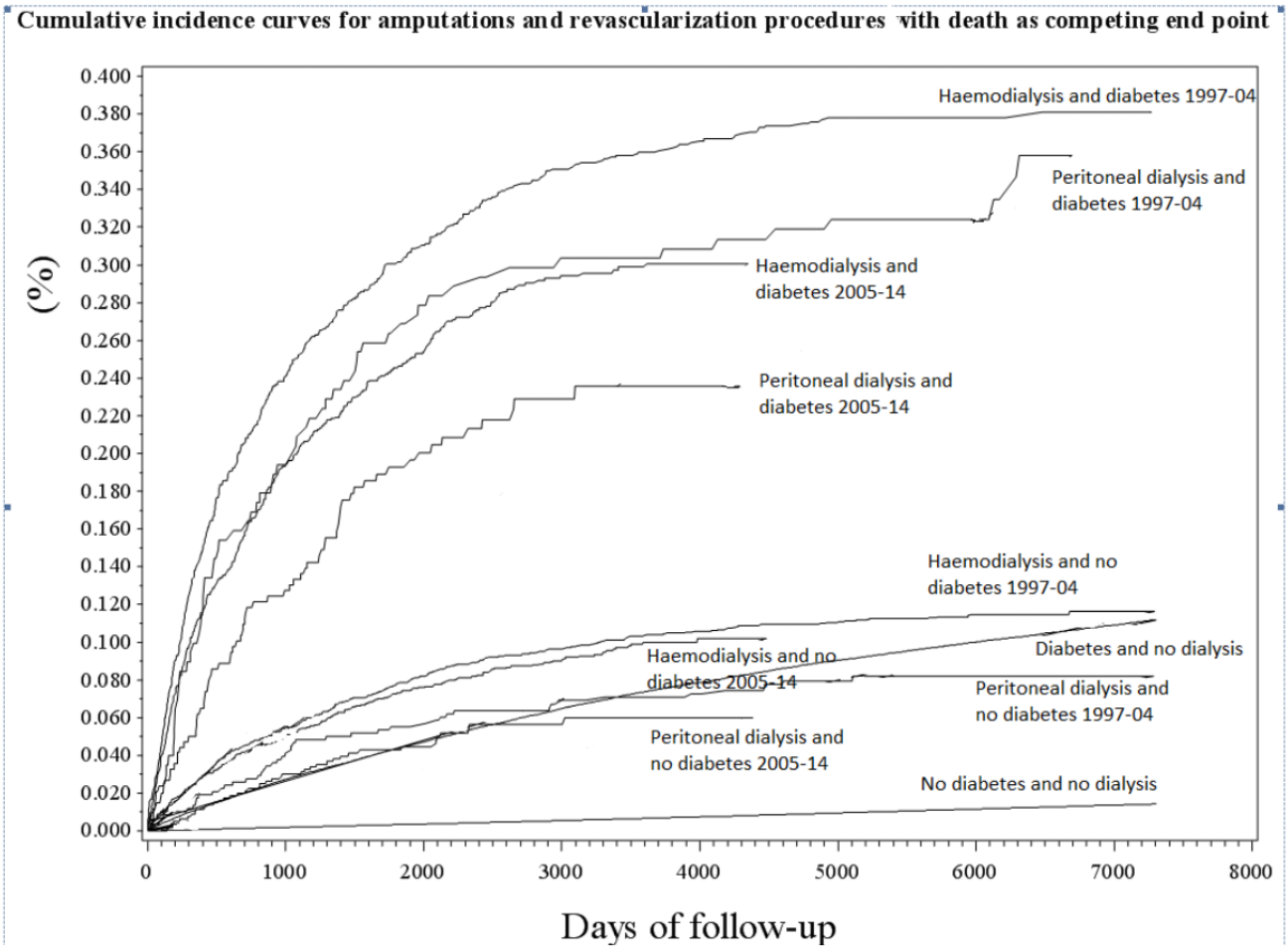

Figure 2: Cumulative incidence curves for amputations and revascularization procedures with death as competing end-point.

In the two time periods age-standardized rates of LEA and LER did not differ between patients on PD without DM compared to patients with DM not on dialysis. Rates were higher in patients treated with HD compared to PD and higher in dialysis patients with DM overall compared to no DM. There was a trend towards lower rates of LEA in those treated with dialysis with DM in the late period. Sensitivity analyses for LEA as lone outcome showed similar results.

Table 3 shows hazard ratios (HR) for LEA and LER respectively and Figure 3 depicts HRs of LEA and LER in combination, stratified by time period, dialysis modality and diabetes state.

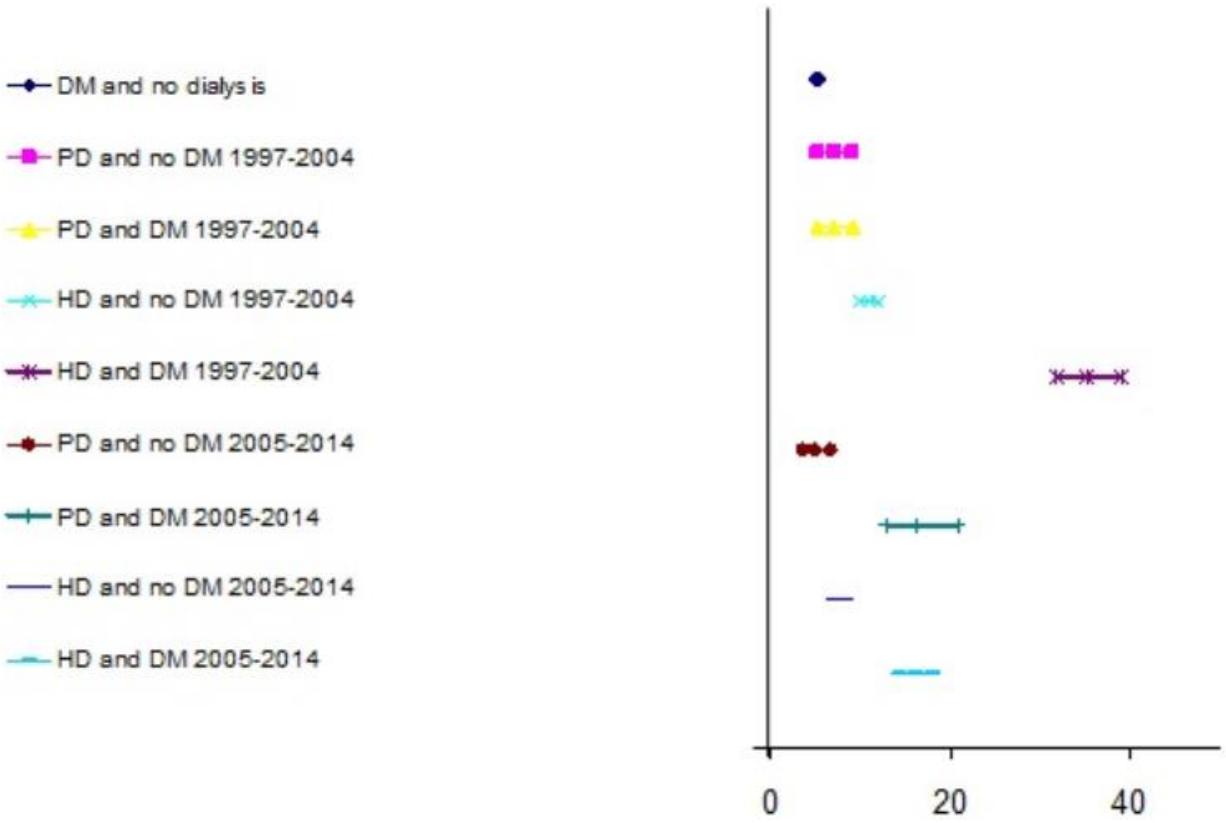

Figure 3: Hazard ratios for risk of lower extremity amputation or revascularization by dialysis modality, state of diabetes and time.

When adjusting for age, sex, comorbidity, prior peripheral revascularization and amputation as well as medication, results remained unchanged.

In the fully adjusted model for the time period 1997-2004, Table 3, there is a HR of LEA for patients on PD without DM of 12 (7.8-18.4) whilst it is more than 6 times higher for those, who have DM 80.8 (62.2-105.0). For patients treated with HD there is a 10-fold difference in HR for those that have DM, HR: 116.5 (103.9-130.7) compared to patients without DM, HR 15.0 (12.8-17.5).

In the second time period, 2004-2014, the same difference is seen between patient in PD with and without DM. For those on HD this difference has been halved from a 10-fold difference to a 5-fold. HR 16.6 (14.1-19.6) HD alone, HR 67.8 (59.6-77.1) HD and DM.

Thus, there is no reduction in risk of LEA for patients on dialysis without DM over time, but a markedly reduced risk for patients on HD with DM.

PD-patients without DM had comparable a risk of LEA or LER compared to DM patients not on dialysis. HD-patients without DM had higher risk of LEA or LER.

Figure 4 shows the smaller incidence rates of LEA/LER in the later time period for patients with DM.

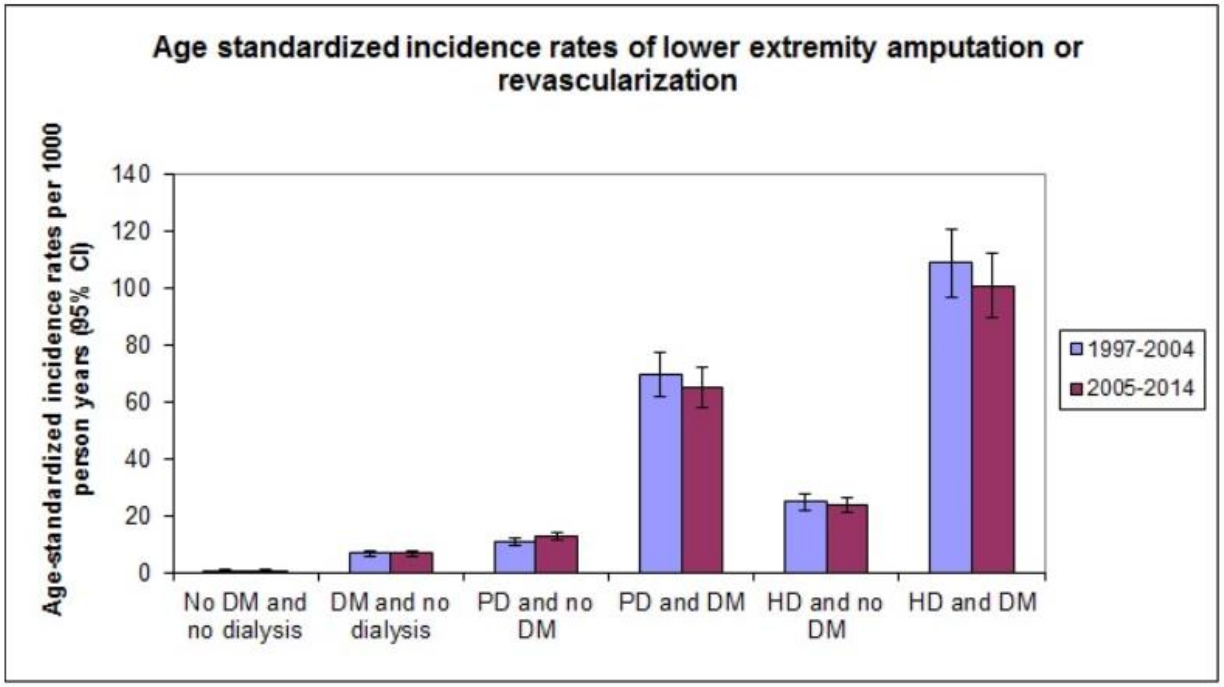

Figure 4: Age-standardized incidence rates of lower extremity amputation or revascularization

Discussion

This paper investigates the rates of LER and LEA in patients treated with dialysis, stratified by dialysis modality and presence of DM compared to the background population. Data were also investigated over time. We found that a great part of patients on dialysis had a high risk of LEA or LER compared to the background population and dialysis patients had a comparable or higher risk compared to diabetes patients not on dialysis.

We found a decrease in LER/LEA in patients with DM over time, but not in patients on dialysis without DM. This indicates that interventions have taken place and that these interventions have proven effective. Other studies have found the same trend[14]. The suggested primary intervention is the formalized attention paid to foot ulcers and peripheral ischemia and neuropathy in the patients with DM. In Denmark since 1981 patients with DM have been screened for peripheral ischemia and neuropathy by podiatricians.

The same prevention programme has not been offered to patients treated with dialysis with no DM. In 2018 121,225 patients with DM had regular assessments of peripheral ischemia and neuropathy assessed by podiatricians by standardized observations. The number of patients, who accept this offer has been increasing since 2012 (personal communication).

O'Hare describes[4] the fact that most dialysis patients are not screened for PAD despite easy access to patients and the high prevalence of PAD in this group of patients. Traditional risk factors for PAD all apply to dialysis patients along with other unconventional factors such as chronic inflammation, and a diversity of biomarkers[4].

Reasons for differences in incidences of LEA/LER in patients on PD vs HD could be the greater comorbidity found in the population treated with HD together with the greater hemodynamic disturbances seen in patients on HD[14]. Patients treated with PD have a greater preserved residual renal function, which could decrease the overall uremic toxin load[15]. Treatment with statins and platelet inhibitors was more common in the second time period. This may also contribute to reduced incidence of LEA and LER[16].

Peripheral ischemia may be silent, because the affected patients often have neural damage along with ischemia[17,18]. This may lead to unawareness of ulcers in the early state, thus letting them progress to larger ulcers with the need for surgical revision and high risk of infection. If ulcers cannot heal the risk of amputation increases and possibility of revascularization decreases[19,20,21].

Identification of the patients at risk is important. All patients with DM should ideally be seen by a podiatrician at intervals already suggested. Screening of peripheral ischemia should be done in all dialysis patients including those with no DM. The patients treated with center HD are in the department 2-4 times pr. week, for at least 3 hours, thus there should be ample opportunity to examine their feet. In the case of patients on PD or home HD, they are seen every 4-8 weeks and routine examination of feet thus possible.

Guidelines have inferred recommendations for routine examination of feet in order to enable early identification of patients at risk.

The time to development of foot ulcers in the uremic state is unknown. We suggest interventions for patients on dialysis without DM of at least same standard as for the patients with DM. When patients are allocated to dialysis treatment a status of their feet should be made in the same manner as for those who have DM. Risk stratification

will decide how often patients should be seen by a podiatrician. The standardized programme could be transferred to patients on dialysis. This comprises yearly status visits and by risk stratification a standardized reaction to either increased awareness of referral to orthopedic or vascular surgeon. Since patients on dialysis have frequent visits to the clinic it is feasible that trained nurses examine and evaluate patients' feet i.e. every 4-8 weeks during dialysis sessions. For those in PD, they should have examinations when they are at the outpatient clinic.

If there is any doubt regarding pulse, referral for measurements of toe pressure should be made. In case of critically low values or ulcers referral to a vascular surgical department is necessary. Ankle/brachial index may be falsely high due to mediasklerosis and the presence of incompressible calcified blood vessels in patients with diabetes or uremia.
For those in HD, treadmills should be offered for patients who lead a physically inactive life.

Conclusion:

Greater awareness and regular visits to podiatricians for patients on dialysis with DM seems to have reduced the need of LEAs. The reduction was not due to greater number of LERs.

Future investigations should be made in order to show if standardized evaluations of feet of patients on dialysis regardless of state of DM will reduce the risk of peripheral ischemia with the detrimental results of LER and /or LEA. It remains to be seen whether PD compared to HD will reduce the risk of peripheral ischemia or differences seen are a result of case mix.

Future studies should investigate the effect of increased awareness and screening of ischemia and neuropathy with regards to reduction of LEA and LER. Interventions could consist of medical treatment and investigate the effect of increase exercise by treadmill.

LIMITATIONS: This is a retrospective study.

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Conflict of Interest Statement

The authors state to have no conflicts of interest.

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